

Remarks

Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are pending in the present application. The following objections and rejections are at issue and are set forth by number in the order in which they are addressed:

1. Claims 1-10, 12, 14-18, 20-26, 28 and 30-41 are provisionally rejected for double patenting over co-pending Application No.: 11/928,464 in view of Schroder;
2. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al.;
3. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al., in view of Schroder et al.;
4. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Primus et al. and Kolb et al.;
5. Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Naldini et al.

The rejections listed above are addressed in order below.

1. Double patenting.

Applicants will file a terminal disclaimer when the other issues are resolved.

2. The claims are not obvious over Mathor in view of each of Burns, Felts; Schott; and Persons

Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as

allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. Applicants respectfully traverse.

A primary step in the obviousness analysis is to “determine whether there was an apparent reason to combine the known elements in the fashion claimed.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007). A rejection for obviousness must include “articulated reasoning with some rational underpinning to support the legal conclusion.” *Id.*, quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). The proper question to ask is whether a person of ordinary skill in the art would have seen a benefit to combining the prior art teachings. *KSR*, 550 U.S. at 424.

The Court also noted that:

[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements *in the way the claimed new invention does* . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Id. at 418-419 (emphasis added); *see also id.* at 418 (requiring a determination of “whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue”) (emphasis added). The *KSR* Court also recognized that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *KSR* at 1739-40 (*citing United States v. Adams*, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966)). “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Gurley*, 27 F.3d 551, 552-53 (Fed.Cir.1994).

Below, Applicants show that the current rejections by the Examiner have no rational underpinning to support the legal conclusion and the prior art, when viewed as a whole, would lead a person of ordinary skill in the art in direction away from the path taken by the Applicants.

A. The current rejection has no rational underpinning to support the legal conclusion

Applicants respectfully submit the current rejections by the Examiner have no rational underpinning to support the legal conclusion of obviousness. This is because the Examiner has

made scientifically unsupportable extrapolations of data contained in the cited prior art references and attempted to utilize references to support arguments that are not relevant to the issue of why the claimed invention is obvious.

The primary mistakes by the Examiner concern the interpretation of the data in Mathor and the Examiner's use of references to support that interpretation. These mistakes are addressed in detail in the attached Fourth Declaration of Dr. Gregory Bleck ("Fourth Bleck Decl.").

First, with respect to Mathor, the Examiner states that:

It is noted that Table 1 (to which Applicant refers to) shows the result obtained with only one keratinocyte clone for each 8 and 15 integration events. Such results cannot be extrapolated to all clones. The Examiner provided evidence to support this statement and it is not clear why Applicant argues that such a statement is sheer speculation and an unsupported extrapolation of the data. It is well established in the art that retroviral insertion is random and that expression level is dependent on the insertion sites (see Mathor et al., of record, p. 10376, column 1; Liu et al., of record, Anal Biochem, 2000, 280: 20-28, Abstract, p. 21, column 1; Stamps et al., of record, Int J Cancer, 1994, 57: 865-874, Abstract, p. 868, column 1, p. 869, Fig. 2). It is noted that Applicant did not indicate why the teachings of Liu et al. and Stamps et al. do not support the Examiner's statement. Applicant points to Table 1 in Mathor et al. for support. In fact, Table 1 in Mathor et al. clearly demonstrates that results obtained with one clone cannot be extrapolated to other clones. Specifically, Table 1 demonstrates that three different clones each comprising 3 copies of integrated vectors secrete different amounts of hIL-6 (180, 150, and 450 ng/10⁶ cells/day, respectively); two different clones comprising 4 copies of integrated vectors also secrete different amounts of hIL-6 (522 and 449 ng/10⁶ cells/day, respectively). Therefore, the Examiner's statement is supported by the art, including the data in Table 1 of Mathor et al. Based on these teachings, one of skill in the art would expect clones with the same number of copies to have different expression levels, and therefore, would know to select multiple clones and look for the high expressing ones.

The issue here is what Mathor teaches to one of skill in the art and whether the data in Mathor indicates to one of skill in the art that cells lines with greater than 20 integrated retroviral vectors (as claimed) would yield higher expression levels than cells lines with 8 or 15 integrated retroviral vectors.

The Examiner argues that the data for one clone cannot be interpreted to other clones. The Examiner is apparently trying to support the argument that other clones that contain 8 or 15 integrations could have had higher expression than what was observed in Mathor. As support for this argument, the Examiner cites the different expression levels observed by Mathor for clones

with 4 or 5 integrations and two references (Stamps and Lui) which teach that retroviral insertion is random and that expression level is dependent on insertion sites. The Examiner then concludes that since other clones could have higher expression levels, a person of skill in the art would expect clones with the same number of copies to have different expression levels and to select multiple clones and to look for high producing ones.

There is a major flaw in the Examiner's reasoning that demonstrates that the rejection has no rational underpinning. The flaw is that just as clones with 15 integrations could have had higher levels of protein expression, such clones could have had lower levels of expression as well. A person of skill in the art would recognize that there is no way to predict, based on Mathor, whether additional clones with 15 (or 20 for that matter) integrated retroviral vectors would have higher levels of expression of a protein of interest than observed in the clones with 8 integrated retroviral vectors. This is confirmed by the Dr. Bleck:

The data in Table 1 of Mathor, which is limited to a maximum of 15 integrations cannot be extrapolated to a situation where there are 20 integrations. It is impossible to do a statistical analysis or curve fit based on the data in Mathor. To provide any other interpretation to the data is not scientifically correct. For example, as shown in Appendix 1, the data could indicate a plateau or upside-down U shaped curve as shown. This is why I have previously said it was not proper to extrapolate the data to cells that have 20 integrations. A person of skill in the art would not do this.

Fourth Bleck Decl. ¶6. The citations to Lui and Stamps do not cure this problem because neither Lui nor Stamps provide any information that can be used to predict whether a cell line containing 20 integrated retroviral vectors will produce more protein than a cell line with 8 or 15 integrated retroviral vectors. Id. The fact that different clones can produce different amounts of protein has no relevance to whether a person of skill in the art would modify Mathor and make clones with 20 or more integrated retroviral vectors.

In fact, the Fourth Bleck Declaration provides a number of scientific papers that show the prior art was very concerned with gene silencing (methylation) of retroviral vectors. In light of this knowledge in the prior art, one of skill in the art would have interpreted the data in Mathor as consistent with showing that increasing retroviral copy number decreases protein expression once a certain number of integrations is reached. Fourth Bleck Declaration, ¶6. When evaluating claims for obviousness, "the prior art as a whole must be considered. The teachings

are to be viewed as they would have been viewed by one of ordinary skill.” *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Accordingly, “[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *Id.* (quoting *In re Wesslau*, 353 F.2d 238, 241 (CCPA 1965)). Applicants respectfully submit that the Examiner cannot pick and choose arguments from references such as Lui and Stamps while ignoring the great weight of the prior teaching of the references provided in the Fourth Bleck Declaration and in the Applicant’s previous responses.

Second, the Examiner states that:

Applicant argues that, since Zielske teaches that use of internal promoters such as CMV results in a plateau of expression at 4 copies per cell, is unexpected in view of the art. This is not found persuasive. Zielske teaches that the limit in transgene expression is related to the particular vector/promoter/transgene/host cell system used in his experiments (p. 926, paragraph bridging columns 1 and 2, p. 929, column 1, third paragraph).

The Examiner’s arguments based on Zielske, alone or in combination with the other references, also fail to provide a rational underpinning for the rejection. The Examiner attempts to limit the impact of Zielske’s statements to a particular vector/promoter/transgene system even though the Examiner has cited this paper as demonstrating the broader concept that increasing copy number increases protein expression. Clearly the reference does not teach that. Zielske’s teaching are consistent with the prior art which establishes that gene silencing was a problem and that protein expression either plateaus or decreases after a certain number of integrations. Fourth Bleck Decl., ¶7. In an attempt to cure this defect, the Examiner relies on Schott et al. to support the fact that “protein expression from retroviral vectors comprising an internal CMV promoter does not reach a plateau when increasing copy number above 4.” However, Schott only describes clones with up to 9 integrated retroviral vectors. Based on the teaching of Zielske and Mathor, one of skill in the art would expect protein expression to decline or plateau after this number of integrations was reached. *Id.*, ¶8. Thus, this paper has no relevance to the issue of whether one of skill in the art would have been motivated to make the claimed cell lines with greater than 20 integrated retroviral vectors. Citation of Schott et al. does not do anything to provide a rational

underpinning for the rejection.

Third, the Examiner cites to Persons et al. for the proposition that “the prior art does teach obtaining stable host cells comprising 20 integrated copies of retroviral vectors.” However, Persons et al. describes the production of retroviral packaging cells that produce infectious retroviral particles. Fourth Bleck Decl., ¶9. These packaging cells are not used for the production of a protein or interest as claimed and are not host cells according to the claims and as defined in the specification. As such, Persons et al. does not address protein production or the impact of including multiple copies of a retroviral vector in a cell line for protein production. Id. Thus, Persons et al. does nothing to add to a rational basis for the rejection either alone or when combined with the other references. Packaging cells are used for producing infectious retroviral particles, host cells are used for producing protein.

Fourth, the Examiner argues that the teachings of Bestor relate to silencing in vivo, not in vitro. However, this is a gross simplification of the teachings of Bestor. As pointed out by Dr. Bleck, many of the references cited by Bestor and those included in Paragraph 4 of his Declaration describe silencing in vitro. Fourth Bleck Decl., ¶10. Bestor was concerned with the problem of gene silencing in vivo because gene therapy requires in vivo expression. However, many of the studies on gene silencing are conducted with in vitro models. Again, the Examiner’s arguments do not provide a rational underpinning for the rejection.

Fifth, the Examiner argues that there is nothing in the MPEP indicating that post-filing art cannot be used to provide evidence of what one of skill in the art would have known before an invention was made and that there is nothing in the MPEP indicating that post-filing art cannot be used to rebut Applicant’s arguments that the prior art would discourage to skilled artisan. Applicants respectfully note that they are unaware of any section of the MPEP that indicates that post-filing art can be used to rebut arguments that true prior art references teach away from an invention. The Examiner is respectfully requested to direct the Applicants to any such section of the MPEP. Applicants respectfully submit that Supreme Court in *Graham v. Deere* state the *scope and content of the prior art* must be considered in formulating an obviousness rejection. (Emphasis added, see also MPEP Section 2141). The *Graham* factors do not include considering post-filing art. Accordingly, post-filing art cannot be used to provide a rational underpinning for an obviousness rejection.

The claims are rejected as obvious over Mathor in view of Burns, Felts, Schott and Persons. For the reasons stated above, a person of ordinary skill in the art would not have seen a benefit to combining the elements of these prior art references in the way that the claimed invention does. As described above, the Examiner has made assumptions about these references that are not scientifically supportable and that would not be made by a person of skill in the art. Accordingly, the Examiner has failed to provide a rational underpinning for the legal conclusion of obviousness. As a result, this rejection should be withdrawn.

B. Considered as a whole, the prior art teaches away from the claimed invention

The prior art, when viewed as a whole, would lead a person of ordinary skill in the art in a direction away from the path taken by the Applicants. Dr. Bleck has provided a number of prior art references that demonstrate the prior art was extremely concerned that the use of retroviral vectors, especially multiple copies of retroviral vectors, would lead to gene silencing in a wide variety of cell types. Fourth Bleck Decl., ¶4. This prior art would have led a person of skill in the art in a direction away from the path taken by Applicants. In particular, the skilled artisan, considering these papers, would have recognized that while introducing a limited number of retroviral vectors into a cell line could increase expression, once more than 10 vectors are introduced there would be gene silencing leading to a plateau or decrease in protein expression from the vectors. As a result, the person of skill in the art would have not introduced the claimed 20 or more vectors into a host cell for production of a protein of interest. As held by the Supreme Court in *KSR*, when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *KSR* at 1739-40 (*citing United States v. Adams*, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966)). Accordingly, the instant rejection should be withdrawn.

3, 4, and 5. The remaining rejections are also defective.

The Examiner also made the following rejections:

- 3) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al., in view of Schroder et al.;

4) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Primus et al. and Kolb et al.;

5) Claims 1-10, 12, 14, 18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. §103, as allegedly being obvious over Mathor et al. in view of each of Burns et al., Felts et al.; Schott et al.; and Persons et al. in further view of Naldini et al.

The additional citations in these rejections of Schroder, Primus and Kolb, and Naldini do not cure the defects noted above for the rejection over Mathor in view of Burns, Felts, Schott, and Persons. In particular, the additional references do not address the scientific deficiencies in the Examiner's arguments described in detail above or rebut or address Applicant's arguments regarding the fact that the prior art as a whole teaches away from the claimed invention. Accordingly, each of these rejections should be withdrawn.

C O N C L U S I O N

All grounds of rejection and objection of the Office Action of July 17, 2009 having been addressed, reconsideration of the application is respectfully requested. It is respectfully submitted that the invention as claimed fully meets all requirements and that the claims are worthy of allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

Dated: September 17, 2009

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